The cornea in young myopic adults

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Abstract

Aims—To further understand the effect of refractive error on the corneal dimensions and function.

Methods—Corneal curvature, corneal thickness, and axial length measurements were performed, as well as specular microscopy and fluorophotometry, on patients with various refractive statuses. 216 subjects, mean age 22.2 (SD 4.2) years, were examined. Patients with previous contact lens wear history, external eye diseases, as well as previous ocular surgeries, were excluded.

Results—The corneas were flatter in eyes with longer axial length ($r = -0.22$, $p = 0.003$). Eyes with more myopic spherical equivalent had longer axial length ($r = -0.90$, $p < 0.001$) as well as less corneal endothelial density ($r = 0.20$, $p = 0.037$). Corneal endothelial density decreased in eyes with longer axial length ($r = 0.24$, $p = 0.019$); however, it correlated neither with corneal thickness ($r = -0.06$, $p = 0.59$) nor with corneal curvature ($r = -0.07$, $p = 0.52$). The corneas had a mean corneal thickness of 533 (SD 29) μm and were thinner in more myopic eyes ($r = 0.16$, $p = 0.021$). The corneas tended to be thinner in eyes with longer axial length. However, the correlation did not reach statistical significance ($r = -0.11$, $p = 0.14$). Besides, there was no significant correlation between the corneal thickness and the corneal curvature ($r = -0.13$, $p = 0.093$) and the endothelial permeability ($r = 0.042$, $p = 0.69$). The corneas with higher endothelial density had larger corneal transfer coefficient ($r = 0.26$, $p = 0.024$) and higher permeability to fluorescein molecules ($r = 0.28$, $p = 0.014$). Nevertheless, the corneal endothelial permeability did not correlate significantly with either the axial length ($r = -0.18$, $p = 0.11$) or the degree of myopia ($r = 0.12$, $p = 0.26$).

Conclusion—Changes in the anterior segments as the eyeball elongates in myopia progression included flatter corneal curvature, decreased corneal thickness, as well as decreased endothelial density. These factors should be considered in refractive surgery.

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Myopia is now a common and almost inevitable pathologic change of the eye, especially in Asian countries undergoing rapid development.[1–4] The myopic prevalence could be as high as to 95% in medical school students.[5] Myopic changes of the eyes include elongated axial length,[1] deeper anterior chamber and vitreous depth,[6] thinner retina with lattice change and higher prevalence of retinal detachment,[7] decreased choroid circulation,[8] as well as decreased sclera thickness and elasticity.[9 10]

Common surgical procedures to correct myopia include radial keratotomy (RK), photorefractive keratectomy (PRK), laser assisted in situ keratomileusis (LASIK), intracorneal ring segment (INTAC), and phakic intraocular lens (PIOL). RK is now mostly replaced by other refractive surgical procedures because of its complications including progressive hyperopic shift,[11] postoperative glare,[12] surgery related corneal endothelial cell loss,[13] and transient change in endothelial barrier function,[13] as well as compromised ocular integrity.[14]

Eyes receiving PRK are less vulnerable to blunt trauma related eyeball rupture than eyes that have undergone RK.[15] In spite of the fact that changes in corneal endothelial cell density after PRK might not be significant,[16] the higher chance of postoperative haze renders PRK less favoured in highly myopic eyes.[17 18] LASIK has been preferred over PRK for its avoidance of photoablation through Bowman's layer and may result in a reduced postoperative haze compared to surface PRK.[17 18] The difference is more significant in high myopic corneas and thus has been a major advantages in these cases. However, LASIK performed on thin corneas may result in inadvertent corneal perforation during LASIK procedure[19 20] as well as subsequent iatrogenic keratoectasia.[21 22] It is thus important to determine if myopic eyes have thinner corneas before surgery.

Phakic IOL has been advocated as another choice for excessively myopic eyes, with less chance of postoperative glare induced by the smaller laser optic zone as well as less chance of induced corneal ectasia. However, the total cumulative loss of central endothelial cells was 8.37% in patients implanted with angle supported PIOL for the correction of myopia 7 years after surgery.[23] The mean cell loss for iris claw PIOL could be as high as 13.42% at 4 years.[24] Because chances of complicated cataract have not been eliminated by the PIOL procedure and endothelial cell loss following cataract surgery might be significant,[25] primary endothelial change related to myopia should be documented. Therefore, the main aim of this study was to further delineate the effect of refractive error on the corneal stroma and endothelium.

Materials and methods

A total of 216 subjects, mean age 22.2 (SD 4.2) years, with an averaged refractive error of −4.17 (SD 5.03) D were included. There were

Table 1 Summary of patients' keratometry, axial length, corneal thickness, and endothelial morphology study parameters

Sex	KM (D)	AL (mm)	Q (μm)	ECD (/mm²)	CV
Male (146)	43.0 (1.3)	25.7 (2.0)	536 (27)	3020 (279)	0.263 (0.033)
Female (70)	43.8 (1.4)	24.3 (1.8)	528 (33)	3009 (194)	0.263 (0.041)
Total (216)	43.3 (1.4)	25.2 (2.0)	533 (29)	3017 (253)	0.263 (0.036)
p Value	<0.001	<0.001	0.091	0.833	0.995

KM = averaged keratometry measurement in dioptres. AL = axial length in millimetres. Q = central corneal thickness by an ultrasound pachymeter. ECD = central corneal endothelial density. CV = coefficient of variation in cell area. Numbers in parenthesis indicate the case number in the particular group.

146 males (aged 22.2 (4.7) years old) and 70 females (aged 22.2 (2.5) years old). None of them had previous contact lens wear or ocular surgery history. Thorough ocular examinations were carried out to exclude cases with ocular pathology except refractive errors and myopia associated chorioretinal changes. The refractive errors averaged −4.90 (5.14) D in males and −2.70 (4.47) D in females. The examinations were divided into two parts.

PART ONE
Cycloplegic refraction and corneal curvature were measured with an autorefractor (Topcon RK-3000). Central corneal thickness was measured with a DGH ultrasonic pachymeter (DGH Technology, Inc, Exton, PA, USA) at 2 to 3 pm on the day of examination. Axial length was measured with an A-scan ultrasound (Sonomed A-1500). The endothelial morphology of the central cornea was recorded with a contact wide field specular microscope (Konan SP-5500) adapted to a video system. Endothelial photographs of good quality were taken into the computer cell analysis system (Bio-optics, Bambi video image analysis system). At least 100 cells were digitised in the computer system and analysed. The mean, standard deviation, and coefficient of variation (CV) were computed for cell area after digitising the apices of each cell. Finally, a baseline scanning for corneal autofluorescence was performed with Fluorotron Master II fluorophotometer (Coherent Medical) fitted with an anterior segment adapter.

PART TWO
On a separate day, at least 3 days after endothelial photography, anterior segment fluorophotometry was performed. The patients were instructed to instil three drops of 2% sodium fluorescein into each eye at 2 am, with an interval of 1 minute between every two instillations. Care must be taken to remove any residual fluorescein around the eyes in the morning of examination. Fluorotron Master II scanning fitted with an anterior segment adapter was performed at an interval of 3 hours starting from 8 am. The endothelial permeability to fluorescein was calculated from the transfer coefficient as follows: permeability = kc.ca × CT × 1.6, in which kc.ca is the cornea to anterior chamber transfer coefficient, as suggested in the Yablonski protocol,[26] CT is the central corneal thickness measured with the ultrasonic pachymeter, and 1.6 is the cornea to anterior chamber equilibrium distribution ratio determined by Jones and Maurice[27] and by Ota *et al*.[28]

ANALYSIS OF DATA
We recorded the following data of each patient (1) central corneal thickness, (2) corneal endothelial density, (3) CV of cell area, (4) endothelial permeability to fluorescein, (5) central corneal curvature calculated by averaging the two major keratometric readings separated by 90°, (6) axial length of the eye ball, (7) spherical equivalent calculated by spherical refractive error plus 0.5 × cylindrical refractive error. Statistical analysis included (1) difference in each parameter studied between males and females, (2) correlation between refractive errors and the endothelial cell density, axial length, CV of cell area, corneal thickness as well as endothelial permeability. Means of different variables between groups were tested by Student's *t* test. A probability of 0.05 was considered statistically significant. Correlation between parameters was tested with a Spearman coefficient of correlation. A two tailed probability of 0.05 was considered statistically significant.

Results
Table 1 summarises the patient's keratometry, axial length, corneal thickness, and endothelial morphology study parameters. The corneal transfer coefficient and permeability for males and females was summarised in Table 2. There was no significant difference in the mean corneal thickness, endothelial cell density, CV in endothelial cell area, and endothelial permeability between males and females. Data in both groups were thus pooled together for a correlation study.

MORPHOLOGICAL STUDIES
Male subjects had flatter corneal surface and longer axial length (Table 1). Correlation between morphological and functional study parameters was summarised in Table 3. The corneal curvature was flatter in eyes with longer axial length ($r = −0.22$, p = 0.003). Eyeballs with more myopic spherical equivalent had longer axial length ($r = −0.90$, p < 0.001) as well as less corneal endothelial density ($r = 0.20$, p = 0.037). There was less corneal endothelial density in eyes with longer axial

Table 2 Summary of patients' cornea to anterior chamber transfer coefficient and endothelial permeability

Sex	Kc.ca × 10³	Perm
Male (146)	4.81 (2.40)	4.09 (1.99)
Female (70)	5.16 (1.68)	4.33 (1.47)
Total (216)	4.92 (2.20)	4.17 (1.84)
p Value	0.476	0.557

Kc.ca = cornea to anterior chamber transfer coefficient. Perm = endothelial permeability ($\times 10^{-4}$/cm). Numbers in parentheses indicate the case number in the particular group.

Table 3   Summary of correlation between morphological and functional study parameters

	AL (mm)	SE (D)	Q (µm)	ECD (/mm²)	CV
K (D)	r = −0.22 p = 0.003	r = 0.07 p = 0.49	r = −0.13 p = 0.093	r = −0.07 p = 0.52	r = −0.09 p = 0.38
AL (mm)	r = 1.00 p =	r = −0.90 p < 0.001	r = -0.11 p = 0.14	r = −0.24 p = 0.019	r = 0.24 p = 0.82
ECD (/mm²)	r = 0.24 p = 0.019	r = 0.20 p = 0.037	r = -0.06 p = 0.59	r = 1.00 p =	r = 0.02 p = 0.84
SE (D)	r = −0.90 p < 0.001	r = 1.00 p =	r = 0.16 p = 0.021	r = 0.20 p = 0.037	r = 0.21 p = 0.83
Perm (×10⁻⁴/cm)	r = −0.18 p = 0.11	r = 0.12 p = 0.26	r = 0.042 p = 0.69	r = 0.28 p = 0.014	r = 0.13 p = 0.28

K = corneal curvature. AL = axial length of the eyeball. ECD = corneal endothelial density. SE = spherical equivalent of refraction error. Perm = endothelial permeability. Q = corneal thickness. CV = coefficient variation of the corneal endothelium cell area. r = Pearson's correlation coefficient. p = two tailed statistical significance by Pearson's correlation test.

length ($r = 0.24$, $p = 0.019$). However, corneal endothelial density correlated neither with corneal thickness ($r = −0.06$, $p = 0.59$) nor with corneal curvature ($r = −0.07$, $p = 0.52$). There was a correlation between the corneal thickness and the spherical equivalent ($r = 0.16$, $p = 0.021$). The corneas were thinner in more myopic eyes (Fig 1). The corneas also tended to be thinner in cases with longer axial length (Fig 2), but the correlation did not reach a statistical significance ($r = −0.11$, $p = 0.14$). The corneal thickness did not correlate with corneal curvature ($r = −0.13$, $p = 0.093$) or endothelial permeability ($r = 0.042$, $p = 0.69$). The CV of cell area correlated neither with axial length ($r = 0.24$, $p = 0.82$) nor with the spherical equivalent ($r = 0.21$, $p = 0.83$).
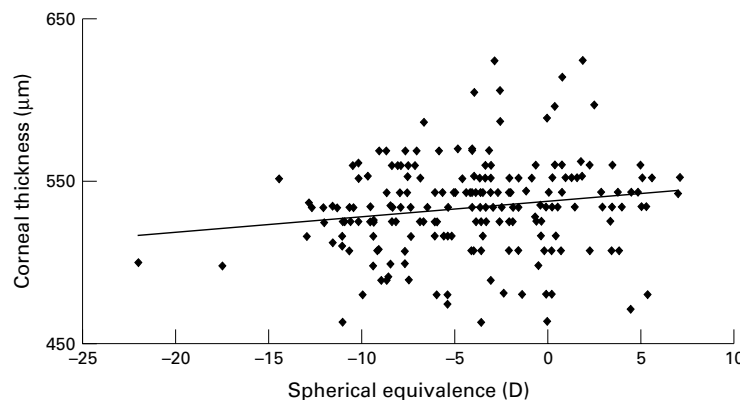

Figure 1   The relation between corneal thickness and refractive errors. The corneas were thinner in more myopic eyes ($r = 0.16$, $p = 0.021$).
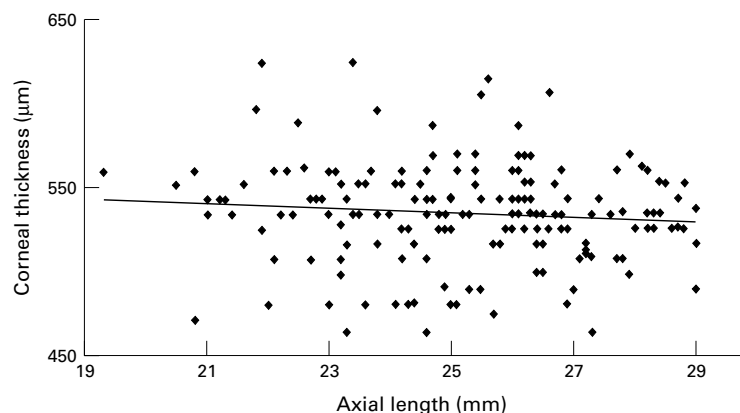

Figure 2   The relation between corneal thickness and axial length. The corneas were thinner in eyeballs with longer axial length, however, the difference was not statistically significant ($r = −0.11$, $p = 0.14$).

FUNCTIONAL STUDIES
The results of corneal transfer coefficient and permeability are summarised in Table 2. The corneas with higher endothelial density had larger corneal transfer coefficient ($r = 0.26$, $p = 0.024$) as well as higher permeability ($r = 0.28$, $p = 0.014$). However, the corneal endothelial permeability did not correlate significantly with the axial length ($r = −0.18$, $p = 0.11$) or degree of myopia ($r = 0.12$, $p = 0.26$).

Discussion
The eyeball elongates during myopia progression. This myopia progression not only makes the globe longer but also makes the sclera thinner,[1][9][10] involving the posterior segment more significantly.[7][29] In addition to the deepening of the anterior chamber found in higher myopia,[6] there are dimensional changes in the anterior segment during myopia progression, but they are less well documented. Goss *et al* reported that eyes with greater vitreous depths tended to have flatter anterior corneal surfaces.[30] In this study, we found that the anterior corneal surface was flatter in eyes with longer axial length. Presumably the endothelial surface area will increase as the axial length elongates and the anterior chamber deepens if the limbal dimension does not change. Because there is no mitotic activity in the corneal endothelium after birth,[31] it is thus conceivable that the corneal endothelial cells will have to flatten to cover the enlarged surface. Subsequently, a reduced corneal endothelial density is expected. In this study, we did find significantly less corneal endothelial density in eyeballs with longer axial length. Since the endothelial cells are capable of preserving function in spite of tremendous enlargement, and generally can maintain corneal function down to cell densities as low as 300–600 cells/mm²,[32] there will be no significant change in the endothelial function in the higher myopic eyes. In this study the correlation between the corneal endothelial permeability and axial length was insignificant.

If the total cornea volume does not increase, we expect that the corneal stroma will become thinner in a similar way as the sclera does in myopia progression. We did note that the cornea was thinner in the more myopic eyes in this study. In Liu's series,[33] the central corneal pachymetry correlated with the mean manual keratometric measurement, simulated keratometry, and intraocular pressure, but no correlation

was noticed between central corneal thickness and the degree of myopia in contact lens wearers. Neither did the central corneal thickness correlate with axial length, age, sex, horizontal corneal diameter, and refraction in Price's series.[34] Cho and Lam found that central corneal thickness decreased with increasing age but not with refractive error or corneal curvatures.[35] In contrast, Tokoro and co-workers found the myopic cornea to be 0.018 mm thinner than the normal controls.[36] Von Bahr discovered a thinner cornea in high myopic eyes.[37] In both Liu's and Price's series, however, the corneal thickness were measured in contact lens wearers. Since great individual variation was noted after wearing contact lenses,[38] this might compound the statistics and partially explain the lack of correlation between corneal thickness and myopia. Furthermore, the time when the corneal thickness was measured was not specified in their studies. This might further compound the results. The corneal thickness has a diurnal variation with the thinnest measurement at 3 o'clock in the afternoon.[39] We thus deliberately measured the corneal thickness at 2–3 o'clock in the afternoon to avoid the variation in corneal thickness. In this study, we found the corneas were slightly thinner in higher myopic eyes in non-contact lens wearers. The correlation between corneal thickness and the corneal curvature was insignificant. This might be attributed to the relatively fewer cases studied.

Alsbirk described an ethnic difference in corneal thickness.[40] The mean central corneal thickness was 550 (33) µm in Price's series of white patients.[34] However, we found thinner corneas in our population (mean 533 (29) µm). This not only confirmed the ethnic difference in the corneal thickness but also aroused further consideration in refractive surgery. Lyle and Jin have reported an incidence as high as 26% of progressive corneal ectasia termed iatrogenic keratoconus following a 52%–70% cutting depth in hyperopic automated lamellar keratoplasty.[41] In Wang's study, posterior corneal bulge following LASIK surgery is correlated with the residual corneal bed thickness and the risk of ectasia may be increased if the residual corneal bed is thinner than 250 µm.[42] Based on previous experience and on the theoretical calculations of Andreassen *et al*, a minimal residual stromal bed thickness of 250 µm was advocated.[43–45] Corneal thinning might be as great as 30–50 µm after wearing contact lens for 13 years.[33 46] In high myopic eyes, more stromal ablation is needed to achieve optical correction, which renders the postoperative cornea even thinner. Because corneal thinning might be significant in higher myopic eyes and a contact lens is usually chosen for myopia correction, the upper limit of laser treatment range will be further reduced when performing LASIK on an Oriental long term contact lens wearer. Yi and coworkers found the corneal flap thickness decreased in thinner corneas and the visual outcome was slightly worse in the thin corneal flaps group.[47] Although a thinner flap is recommended to achieve more optical correction in higher myopia cases, the visual

result might thus be more guarded in the Oriental higher myopic eyes because of the relatively higher chance of having a thinner flap as well as subsequent corneal striae and striae related visual disturbance. It is not known whether the refractive effect of intracorneal ring segment differs in the thinner Oriental corneas. With a high myopic rate of 20% at the age of 18,[1] refractive procedures for myopia correction other than LASIK might be more important in the Oriental population in the future.

Sodium fluorescein molecules pass through the intercellular space. Higher endothelial density has more intercellular contact areas that are permeable to fluorescein molecules. It was documented that the corneal endothelium is more permeable in cases with higher endothelial density in normal eyes.[46] We further found a decreased cornea to anterior chamber transfer coefficient as well as permeability in cases with less endothelial density in this study. Changes in the corneal endothelial morphology and barrier function were noticed after radial keratotomy.[13] However, it remains unknown whether the endothelial permeability changes following excimer laser surgery.

In conclusion, changes in the anterior segments as the eyeball elongates in myopia progression included flatter corneal curvature, decreased corneal thickness, as well as decreased endothelial density. These factors should be taken into account before performing refractive surgeries.

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